Embolic risk of the different stages of carotid bifurcation balloon angioplasty: An experimental study

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Purpose: Embolic events during carotid angioplasty are a challenging problem. This experimental study was undertaken to determine the embolic risk after each stage of carotid angioplasty procedure.

Methods: Five ex vivo carotid artery balloon angioplasties were performed on fresh carotid specimens. The carotid specimens were obtained from five patients who underwent an internal carotid artery bypass for stenosis >75%. Before the endovascular maneuvers and after each stage of the procedures, the specimens were flushed with 20 mL of saline solution. Small particulate emboli (diameter, <60 μm) were searched in all the effluents according to the Coulter technique. After this procedure, each effluent was also submitted to scanning electron microscopy.

Results: When the stenosis was crossed with the guidewire or the balloon catheter, the number and the mean diameter of embolic particles did not change with three plaques (CP1, CP2, and CP3) and were increased with two plaques (CP4 and CP5). The maximal size of particles was 220 μm (CP5). After balloon angioplasty, the number and the mean diameter of particles increased with CP1, CP2, and CP3. With CP4 and CP5, the number of particles decreased, but their size increased. The maximal size of particles was 1100 μm (CP4).

Conclusion: Carotid balloon angioplasty generates embolic particles after each stage of the procedure. Techniques of prevention should then be effective from the initial step of the angioplasty procedure, and the selection of patients for carotid angioplasty remains crucial. (J Vasc Surg 2000;31:550-7.)

Balloon angioplasty is now widely used to treat short peripheral and coronary arterial stenoses. In cerebral arteries and especially at the level of carotid bifurcation, balloon angioplasty remains controversial despite the theoretic benefit of endoluminal procedures, even with primary stenting. Cerebral embolic events are at risk of stroke and constitute the most challenging problem of carotid angioplasty.[1] Recently, Ohki et al[2] developed an ex vivo model in which endarterectomy specimens of carotid bifurcations were encased in expanded polytetrafluoroethylene (ePTFE) wraps to analyze the risk for embolic events associated with carotid balloon angioplasty and stenting. This model demonstrated the higher risk of emboli associated with tight stenoses and low echogenicity plaques.

We developed another ex vivo model using fresh carotid bifurcations explanted during carotid bypass graftings to quantitatively analyze embolic particles that were generated at each stage of the angioplasty procedure. Another characteristic of this new model was the performance of the angioplasty on nonendarterectomized carotid bifurcations. This model was used to assess the number of particles and their size and the subsequent risk of stroke before the procedure, after the lesion was crossed with a

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guidewire, after the placement of the balloon catheter, and after balloon angioplasty.

MATERIAL AND METHODS

Five ex vivo carotid artery bifurcation balloon angioplasties were performed between January and June 1998. The carotid bifurcations used in these experiments were obtained from five patients who were undergoing a common to internal carotid bypass graft to treat a symptomatic carotid bifurcation stenosis >75%. In these five patients, the indication for a bypass procedure was a carotid bifurcation stenosis measuring between 2 and 2.5 cm in length that resected the middle and the distal part of the common carotid artery (CCA) and the juxtacranial internal carotid artery (ICA). The carotid bifurcations could be resected because our standard bypass technique includes a reimplantation of the external carotid artery (ECA) in the graft. During the same period of time, 42 patients underwent standard carotid endarterectomy procedures.

Characterization of carotid lesions. Carotid lesions were characterized according to preoperative angiographic images and duplex ultrasonographic scans. Percentage stenosis was calculated according to the North American Symptomatic Carotid Endarterectomy Trial criteria.[3] The presence or absence of plaque ulceration was determined by an evaluation of angiograms and duplex studies.

Surgical procedures. Patients underwent the operation under locoregional anesthesia. The carotid bifurcation was exposed through a standard presternocleidomastoid incision. The patients were given 50 U/kg sodium heparinate, and the CCA and ECA were clamped. In the absence of any neurologic event over a 5-minute test period, the ICA was clamped, and the carotid artery bifurcation was excised. The excised arterial specimen included the distal 5 cm of the CCA, the proximal 3 cm of the ICA, and approximately 1 cm of the ECA. A 6- or 7-mm diameter ePTFE graft was then interposed between CCA and ICA. Both anastomoses, proximal and distal, were done end-to-end with 6-0 monofilament sutures. The ECA was then reimplanted in the graft, directly or using a short ePTFE interposition graft. We routinely use this technique for carotid bypass grafting for two reasons: (1) hemodynamic conditions are probably better with such an "anatomic" bypass graft than with a simple laterotherminal bypass graft, and (2) endarterectomy of the ECA is not necessary, reducing the subsequent risk of occlusion.

Preparation of the carotid specimen. Immediately after excision of the carotid artery bifurcation, the ECA was ligated just distally to the origin of the superior thyroid artery. The excised arterial specimen was then gently rinsed with saline solution to remove blood residues and kept in normal saline solution until the ex vivo angioplasty procedure, which was performed in the operating theater immediately after the end of the surgical procedure.

Ex vivo balloon angioplasty. Fresh carotid specimens were fixed over a radiolucent plate with the use of polypropylene sutures. A 7F sheath (Terumo Corporation, Tokyo, Japan) was then connected to the CCA with a ligature to secure the specimen for subsequent studies. The extremity of the ICA was kept open. The experimental complex was then placed over a radiolucent operating table.

Ex vivo angiography of each carotid specimen was performed before the intervention by means of an injection of contrast material into the CCA through the sheath and imaging with a C-arm fluoroscope (OEC Medical Systems, Salt Lake City, Utah). A 0.018-inch hydrophilic guidewire (Terumo Corporation) was passed through the stenosis under fluoroscopic guidance. A 5-mm × 2-cm angioplasty balloon (Sub-4; Medi-Tech/Boston Scientific, Natick, Mass) was then advanced over the wire and correctly positioned with fluoroscopic guidance. Angioplasty was performed with three inflations of the balloon up to a pressure of 7 atm for 10 seconds. Angiograms were obtained after the balloon dilatation.

Collection of embolic particles. Before the endovascular maneuvers and after each stage of the experimental procedure, the specimens were flushed with 20 mL of saline solution infused over 2 seconds through the sheath. The effluent of each flush was collected at the open extremity of the ICA. Samples were then obtained before any endovascular maneuver (E0), after guidewire placement (E1), after the positioning of the angioplasty balloon (E2), and after the balloon angioplasty (E3). E0 and E3 samples were always obtained before angiographic controls. Each sample was supplemented with 2 mL of crude formaldehyde and kept at 4°C before analysis.

Analysis of embolic particles. Particulate emboli were searched in all the effluents. Effluents were first treated to count small particles according to the Coulter technique. Three drops of Zap oglobine (Beckman-Coulter, Margency, France) were added to the effluent to destroy the erythrocytes. Small particles were then counted in each effluent with the use of a Coulter Multisizer (Beckman-

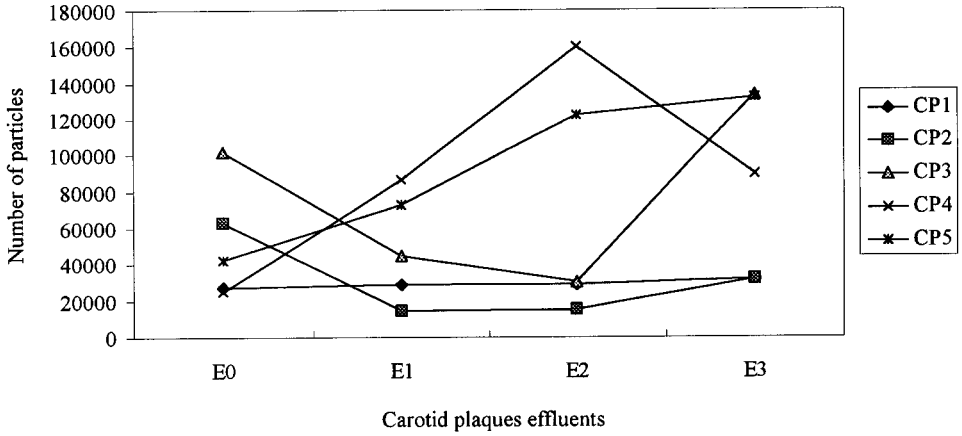

Fig 1. Number of small particles (<60 μm maximal diameter) detected by the Coulter technique.

Coulter) and a 100 μm filtering orifice. With this calibration, counts were reliable for particles less than 60 μm in diameter. Two counts were performed on each effluent to determine the number of particles that were less than 60 μm in diameter and the number of particles that were less than 20 μm in diameter. With these two thresholds of measure, three parameters were defined to evaluate and compare the number and the size of the particles in the effluents: (1) the total number of particles measuring less than 60 μm in diameter, (2) the number of particles between 20 and 60 μm in diameter, and (3) the mean diameter of the detected particles.

After this procedure, each effluent was filtered through a sterile cellulose acetate membrane calibrated to 0.45 μm. The membranes were then removed from the filters, vacuum-dried, and gold-palladium coated according to standard techniques for scanning electron microscopy (SEM). Each membrane was examined in a scanning electron microscope (JSM 840; JEOL USA Inc, Peabody, Mass). The diameter and the morphologic features of the largest particles were analyzed at the magnifications of × 50 and × 250.

RESULTS

Characteristics of carotid lesions. All of the patients underwent an ICA stenosis of more than 75%. In patients 1, 2 and 3, the carotid plaques (CP1, CP2 and CP3, respectively) were smooth and localized to the carotid bulb, without ulceration and irregularities. In patients 4 and 5, the carotid plaques (CP4 and CP5, respectively) were irregular on the angiograms. CP4 was located at the tip of the carotid bulb, which was large and irregular; and CP5 was ulcerated on the angiogram and duplex scan.

Surgical procedures. All of the patients underwent a carotido-carotid bypass graft with a direct reimplantation of the ECA. No perioperative complication was observed, and the postoperative course was uneventful in the five patients. All of the patients underwent postoperative angiography or a duplex scan that demonstrated the patency of the carotid bypass graft.

Ex vivo balloon angioplasty. The time interval between the carotid bifurcation excision and the ex vivo balloon angioplasty procedure varied between 60 and 90 minutes. Carotid balloon angioplasty was successfully performed on all the carotid artery bifurcation specimens. In all the specimens, a residual stenosis of more than 30% was observed after the balloon angioplasty.

Counts and size of embolic particles. All of the E0 effluents contained between 25117 (CP4) and 101900 (CP3) particles (Fig 1). The mean diameter of these particles varied from 3.62 (CP5) to 6.5 μm (CP1; Fig 2). SEM examination of these E0 particles predominantly showed platelet aggregates. When the arterial lesion was crossed by the guidewire (effluent E1) or when the balloon catheter was positioned (effluent E2), the number (Fig 1) and the mean diameter (Fig 2) of the embolic particles did not change with CP1, CP2, and CP3. With CP4 and CP5, the number of embolic particles was higher after these maneuvers (Fig 1), but their diameter was unchanged (Fig 2). The maximal size of E1 particles (Fig 3) measured by SEM was 112 μm (CP2; Fig 4). The maximal size of E2 particles (Fig 3) was approximately 220 μm with CP5 (Fig 5). After balloon angioplasty (effluent E3), the number of embolic particles generated by carotid lesions remained

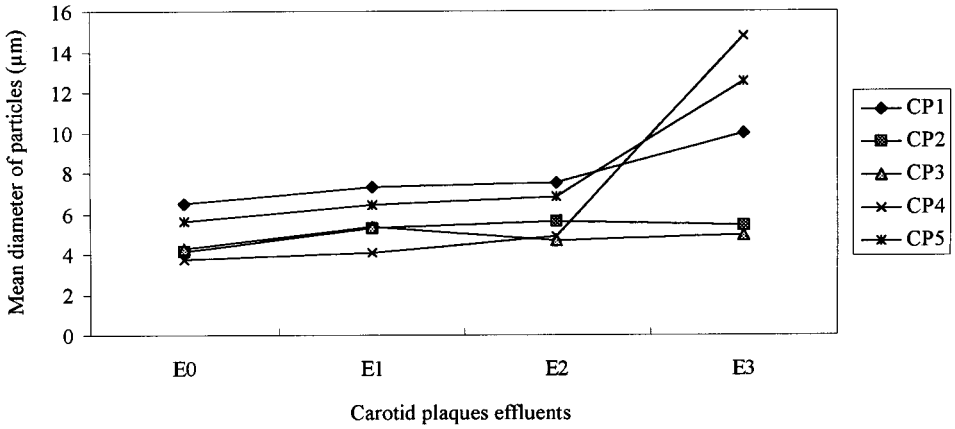

Fig 2. Mean diameter of small particles (<60 µm maximal diameter) detected by the Coulter technique.

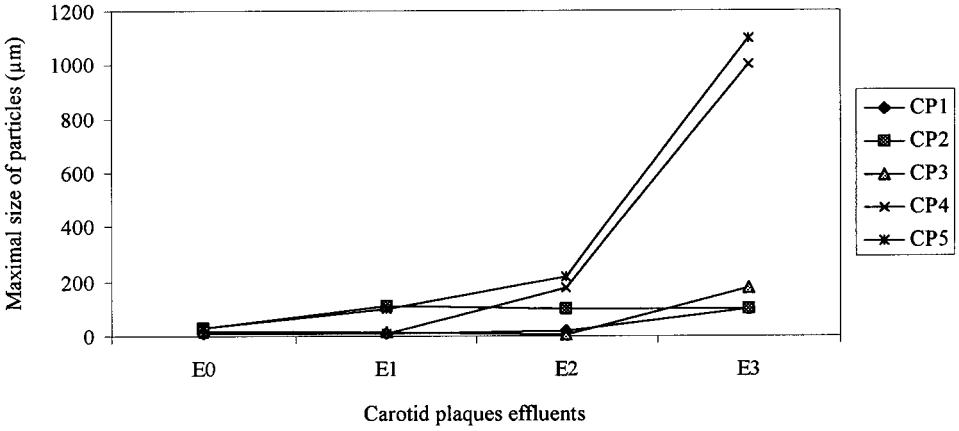

Fig 3. Maximal size of particles detected by SEM examination.

unchanged with CP1, but it moderately increased with CP2 and highly increased with CP3 (Fig 1). With CP4 and CP5, the number of embolic particles decreased in E3 compared with E2 (Fig 1). The mean diameter of the E3 embolic particles increased to reach 14.78 µm in CP4 (Fig 2). Moreover, the number of embolic particles with a diameter between 20 and 60 µm highly increased after balloon angioplasty (Fig 6). The maximal sizes of E3 particles observed in SEM (Fig 3) were 1000 (CP4) and 1100 µm (CP5), with several particles measuring between 100 and 800 µm (Fig 7).

DISCUSSION

Balloon angioplasty generates embolic particles,[1,4-8] which consist of atherosclerotic debris, calcified material, endothelial fragments and microthrombi composed from platelets, fibrin, and cholesterol. Air bubbles may also migrate during the procedure. Such embolic events have been reported to occur in 3% to 5% of coronary and peripheral balloon angioplasties.[1,4,6] This embolic risk appears higher after carotid bifurcation balloon angioplasty,[9,10] and several series reported cumulative perioperative stroke and death rates that range between 5.3% and 9.7%.[8,11-16] In these series, most of the strokes were believed to be caused by multiple embolic occlusions of the middle cerebral artery.[12,17] With the use of transcranial Doppler ultrasound scanning, it was also shown that numerous embolic particles could be detected during carotid balloon angioplasty.[1,8,9,18,19] Experimental models demonstrated the embolic risk of balloon angioplasty.[4-6,20] Nevertheless, these models did not reproduce the characteristics of human atheromatous stenoses.[4,6]

De Monte et al[21] searched for particulate emboli after carotid balloon angioplasty. In their study, atheromatous and acellular debris represented only 0.0055% of the total volume of the postangioplasty effluent. However, their search was done during ret-

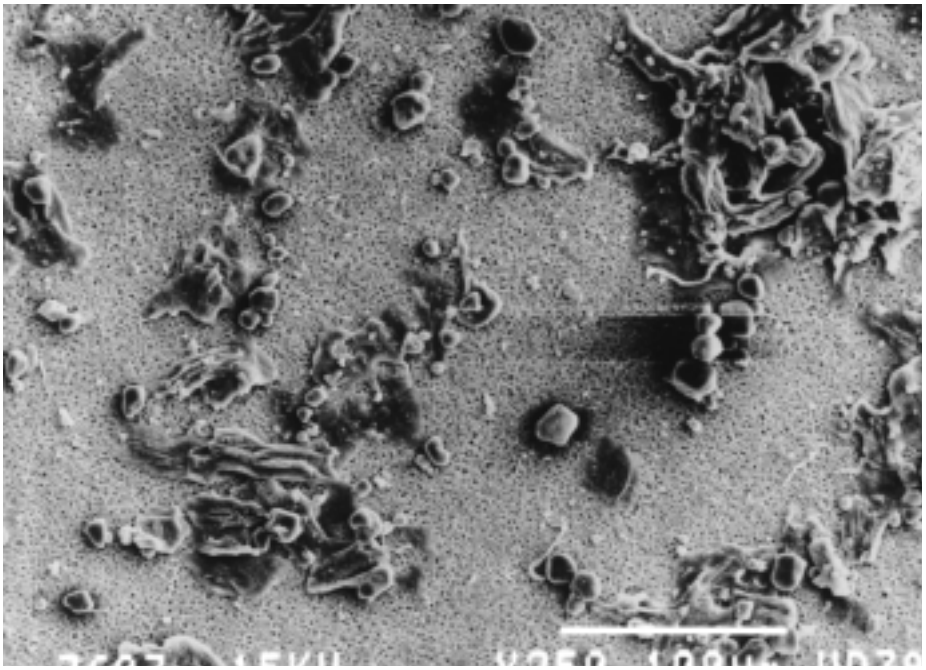

Fig 4. Particles shown by SEM examination of the E1 effluent collected after crossing the CP2 carotid plaque with a guidewire. (Original magnification, ×250.)

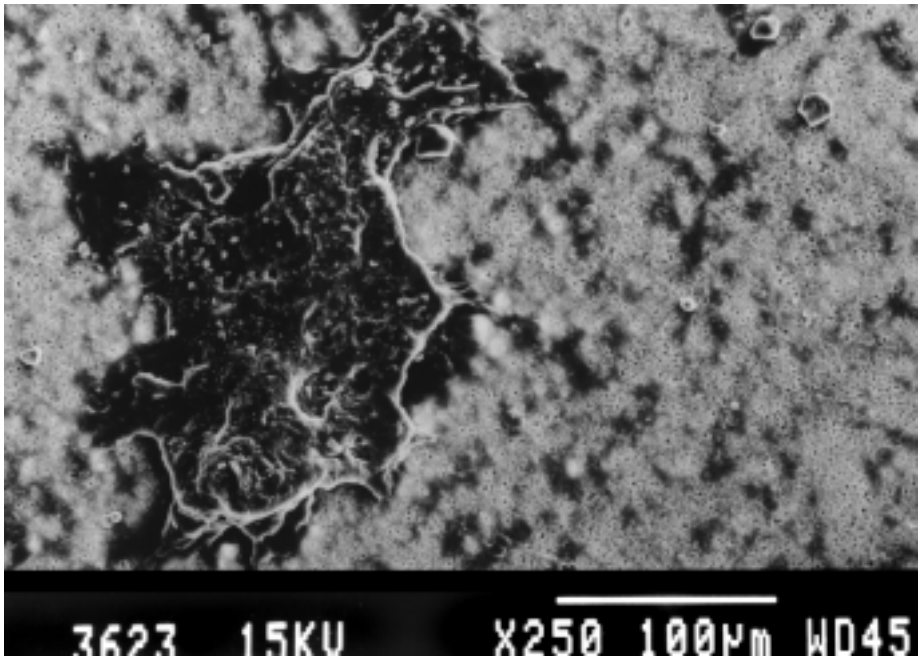

Fig 5. SEM examination of the E2 effluent collected from the CP5 specimen after the balloon catheter was positioned shows a large embolic particle. (Original magnification, ×250.)

rograde balloon angioplasty of the proximal CCA, where the morphologic characteristics of plaques are very different from those observed at the carotid bifurcation. More recently, Ohki et al[2] developed an ex vivo human model to study the embolic potential of carotid bifurcation angioplasty and stenting. In these experiments, they removed endarterectomy specimens as casts of carotid bifurcation that were encased in an ePTFE wrap to re-create the adventitia. Balloon angioplasty with stenting was then per-

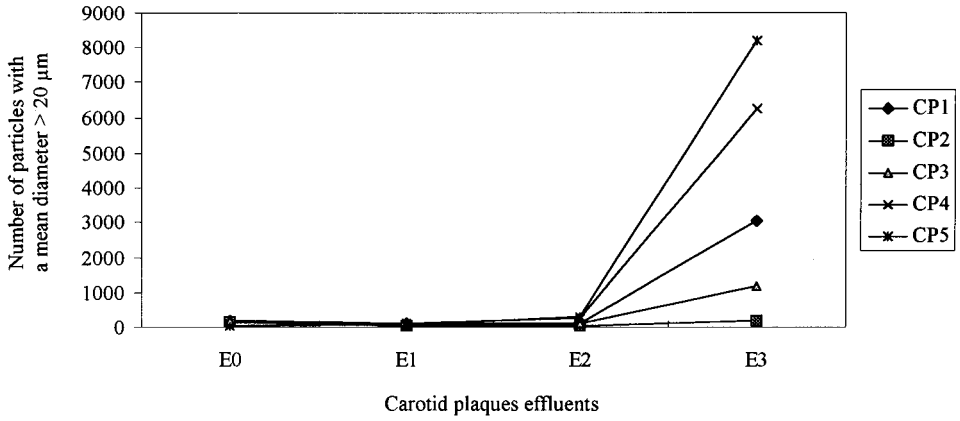

Fig 6. Number of small particles with a diameter between 20 and 60 µm.

formed, and the effluent from each specimen was filtered for embolic particles larger than 120 µm. The embolic risk of balloon angioplasty was correlated with plaque characteristics and the severity of stenosis. This study clearly showed that echolucent plaques and plaques with stenosis of 90% or more generated a higher number of embolic particles after balloon angioplasty and stenting. Embolic particles essentially consisted of atherosclerotic debris.

This investigation was designed to study the risk for embolic events according to the different stages of carotid artery bifurcation angioplasty. In this model, the use of fresh carotid bifurcation specimens allowed for the performance of the balloon angioplasty of carotid plaques left in the arterial wall. Moreover, elasticity of the human carotid arteries was maintained. Balloon angioplasty was performed according to the technical principles advocated by some authors.[1,17] However, in our model and in the study reported by Ohki et al,[2] air bubble emboli were not searched for.

In this study, particulate emboli were detected after each stage of the angioplasty procedure. The Coulter technique was chosen for its ability to detect small particles. SEM was used to detect and calibrate the largest particles to predict the clinical significance of these particulate emboli. The size of most embolic particles generated by carotid balloon angioplasty was less than 60 µm, with many platelet or cholesterol microthrombi. These small microthrombi could be expected to be trapped in the cerebral capillaries and the cortical arteries of the pia mater with infraclinical consequences.[1] However, the progressive neuropsychic sequelae of such microemboli are unknown, and clinical tests would help to better define their consequences.[1]

Particulate emboli generated by the placement of the endoluminal guidewire and the balloon catheter were due to the parietal trauma when the lesion was crossed.[1] Embolic particles detected after positioning the guidewire could occlude peripheral cortical arteries, thalamic arteries, and precapillary arterioles. Particles detected after positioning the balloon catheter could occlude the lumen of third generation cortical arteries. With such particles, the neurologic risk depends on the number and the frequency of the emboli. The risk of emboli as early as the endoluminal guidewire crosses the lesion or when the balloon is positioned raises questions about protective techniques with the use of coaxial catheters, as proposed by Theron et al.[11] These techniques require the pass through the stenosis with an occlusive microballoon before dilation. The diameter of the balloon catheter used by Theron et al (0.8 mm) is about twice the size of a 0.018-in (0.45 mm) guidewire. According to the results of this study, the parietal trauma caused by an occlusive catheter crossing a tight or irregular stenosis could easily generate embolic events. Similarly, as emphasized by Brown,[1] primary carotid stenting could also be at risk of parietal trauma and emboli. After balloon angioplasty, particulate emboli were detected whatever the morphologic characteristics of the atherosclerotic plaque. The size of most particles detected by SEM ranged from 200 to 500 µm. These results are in accordance with transcranial Doppler ultrasound scanning and show that the size of most embolic particles generated by balloon angioplasty is less than 400 µm.[8] Such particles could occlude cortical arteries and most of the perforating arteries of the central gray nuclei and of the hypothalamus. The size of the largest particles

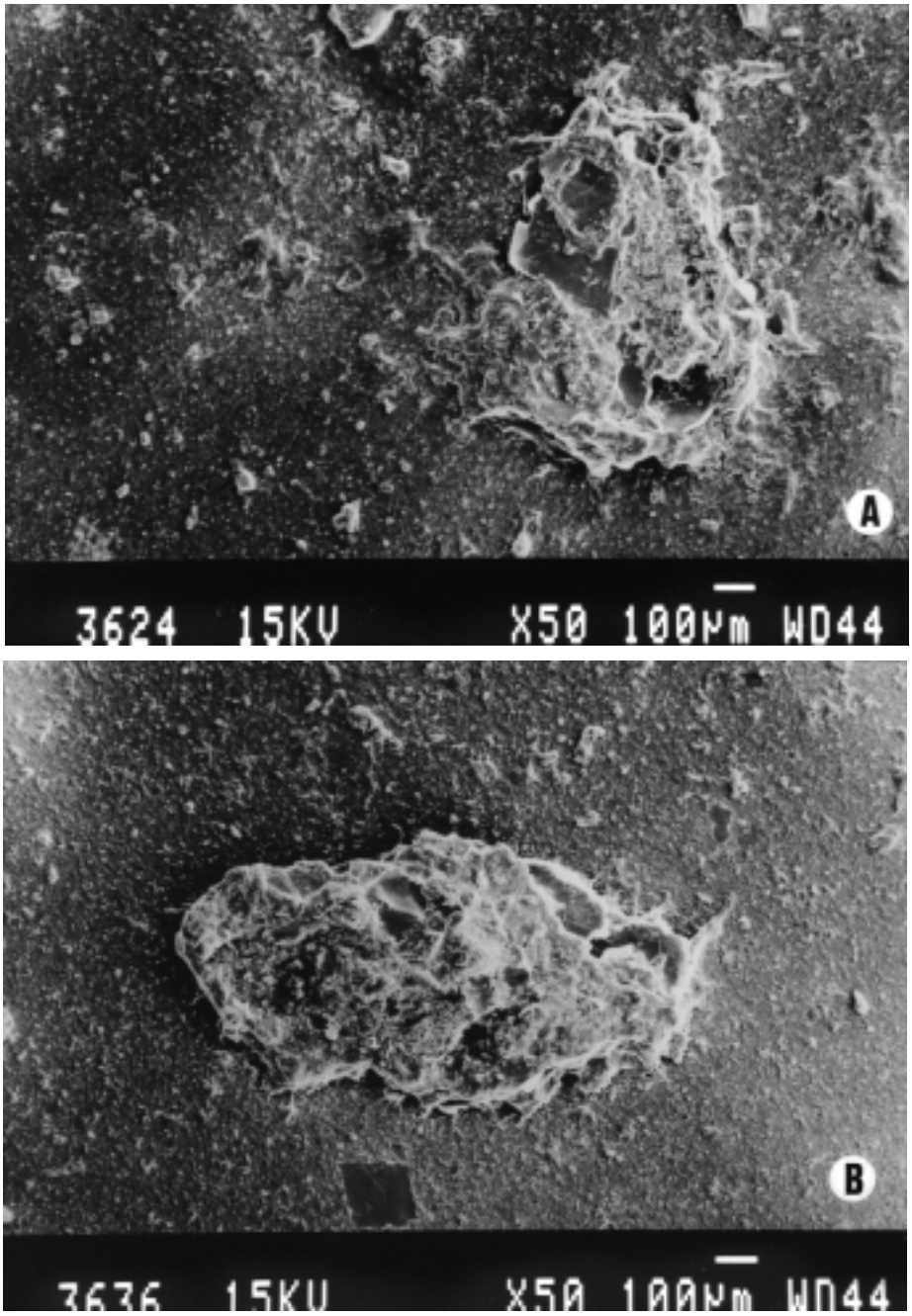

Fig 7. Particles demonstrated by means of SEM examination of the E3 effluents collected from CP4 (A) and CP5 (B) plaques after balloon angioplasty. (Original magnification, ×50.)

detected after balloon dilatation was between 1000 and 1500 µm. In the model developed by Ohki et al,[2] the maximum size of the particles was 2100 µm. The neurologic risk of particles measuring more than 1000 µm is certainly high because they can occlude cerebral arteries and communicating arteries of the Willis polygon. Downstream, these particles could also occlude the cortical arteries of the first dichotomies. In this model and in the model by Ohki et al, these large particles were scarce, but a single emboli of that size could induce a stroke. Moreover, these particles could be released through the large interstices of some stents, which suggests the advantage of covered stents in carotid angioplasty.

CONCLUSIONS

Even if the extent to which this model is exactly translatable to clinical circumstances is unclear, it demonstrates that carotid bifurcation balloon angioplasty is at risk of emboli at each stage of the procedure. Therefore techniques of prevention should be effective from the initial step of the angioplasty procedure. At the present time, occlusive balloons and stents are the recommended protective techniques. However, even with these techniques, primary crossing of the carotid plaque remains necessary, with a risk of parietal trauma, especially with irregular or tight stenoses. The selection of patients for carotid angioplasty is then crucial.

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